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Refractory Heart Failure

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• Any patient with so-called "refractory" heart failure should be looked upon as suboptimally handled. The patient should be studied for possible development of new disturbances, either inside or outside the vascular system, which, at the same time, have a bearing upon the heart failure.

The entire therapeutic program should be reviewed to be sure that all aspects of therapy have been evaluated satisfactorily and established optimally. If diuretics, especially mercurial diuretics, have been given, the possible complications of such therapy, particularly in terms of electrolyte imbalance, should be considered. It is only through a general survey of the patient for an evaluation of these factors that they may be found and therapy instituted to minimize or eliminate them.

THE EARLY STAGES of congestive heart failure usually can be well controlled without difficulty. It is during the course of the disease that, sooner or later, there often comes a time when the therapeutic program, even when carried out in a seemingly satisfactory fashion, is no longer effective. The patient is then said to have "refractory heart failure." It is natural to assume at this point that the cardiac reserve has been so reduced that there is no longer sufficient active heart muscle to carry on the necessary activities of life even at rest, and that even with treatment a satisfactory level cannot be reached to maintain normal circulatory function. If a patient reaches this state, despite all the methods of treatment being applied optimally, he then truly has refractory heart failure. However, it frequently happens that the state of refractoriness is assumed even though the previously described circumstances above do not prevail. The so-called refractory heart failure may be the result of suboptimal handling of the patient. It is well, therefore, in all instances of "refractory heart failure" to consider possible factors in the patient which might be conducive to suboptimal therapy.[3]

The patient should receive "optimal" treatment. What is optimal for one patient may not be optimal for another. A physician, when confronted with a patient having seemingly refractory heart failure, should be prepared to review the primary cardiac diagnosis, to search for development of new noncardiac states, and to review his therapy to note its shortcomings in any sphere.

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REVIEW OF DIAGNOSIS

It is important to reevaluate the primary diagnosis, to be sure that it is satisfactory, and to know definitely that no new factor has been introduced.

Primary Diagnosis. It is possible that the diagnosis of congestive heart failure may have been in

error. Not only must noncardiac states, which cause edema, such as nephrosis or nephritis, be ruled out, but in addition it must be made certain that the congestive heart failure is produced by a cardiac state amenable to the usual treatment. Certain disturbances in cardiac function are amenable to treatment based upon the etiologic factors. This is true of myxedema, hyperthyroidism, beri-beri and various types of active myocarditis. Certain other cardiac states, such as constrictive pericarditis and chronic tuberculous pericarditis, must be treated by removal of the constricting influence, be it fibrous tissue or fluid. Where an anatomic stricture can be relieved by operation, as in mitral stenosis, or where abnormal channels for blood can be closed, as in patent ductus arteriosus, such states are best treated by the surgical procedure applicable to the particular case. Patients may show remarkable degrees of recovery following procedures to correct such defects when they have responded inadequately to treatment for congestive heart failure previously.

Progress in and New Developments in the Cardiac State. Refractoriness in therapy may result from new developments during the course of the treatment. For example, myocardial infarction may cause the reappearance of congestive heart failure which has been previously under control. At times in older patients the onset of myocardial infarction may not be manifested by significant pain, and acute heart failure developing from it may mask to some degree minor manifestations of chest pain. It is well, with onset of congestive heart failure in older persons particularly, if heart failure has been present before and brought under control, to suspect possible myocardial infarction and to take measures to establish its presence or absence.

The onset of arrhythmia, especially if it is very rapid, may throw a patient into congestive heart failure when he has been carrying on adequately previously. The onset of auricular flutter or fibrillation may, if the loss of cardiac reserve has reached a critical level, make it impossible to control the congestive state unless the arrhythmia is controlled or stopped. Such arrhythmia may develop insidiously without the patient's knowledge, particularly in older persons. Other conditions which throw added strain upon the myocardium, such as hypertensive states or exacerbations of such states, reactivation of rheumatic fever, or the effects of developing bacterial endocarditis, may similarly interfere with compensation and bring about heart failure that is difficult to control. Again, therapy must be directed at the newly developed factor.

Progress in and New Developments of Noncardiac States. Disease outside the heart may interfere with therapy. At times the development of anemia, for example, may disrupt an effective program. Hemoglobin values below 50 per cent would produce oxygen deficiency in tissues if adjustments were not made in the cardiovascular system. Increase in cardiac output is a compensatory mechanism but this throws an increased load upon the heart. If this strain is sufficient to produce decompensation in the damaged heart despite treatment, the patient will go into heart failure. Correction of the anemia may bring the patient out of congestive heart failure. Pulmonary infarction, a common accompaniment of congestive heart failure, is not infrequently a factor which makes the program for congestive heart failure ineffective. Pulmonary infarction is not always easy to recognize. Its less florid clinical pictures are frequently misdiagnosed, particularly when low grade fever and some tachycardia are the chief findings. Even when pulmonary findings are present they may be misinterpreted as pneumonia or as recurrent pneumonia. So called "masked" hyperthyroidism is also an unrecognized factor at times in refractory heart failure. In older patients, particularly those having auricular fibrillation, manifestations of hyperthyroidism are not always clearly evident or are not always a dramatic part of the symptomatology and clinical picture.

Because of digitalis effects, low salt diets, or other circumstances a patient with congestive heart failure may enter a stage of malnutrition or starvation. Refractoriness to treatment may develop upon this basis, especially if protein malnutrition is extensive. In these circumstances it is necessary to treat the patient nutritionally until he improves from that standpoint. The previously used aspects of the program may then be reinstituted.

It is clear that the development of so-called refractory congestive heart failure requires review not only of the patient's primary diagnosis, but also of the present status of the individual to determine whether or not an additional factor, which is important either in reducing cardiac reserve or in increasing strain upon the myocardium, has appeared.

THE REVIEW OF THERAPY

There may be inadequacies in and complications to therapy which lead to suboptimal handling of the patient. As already stated, early in congestive failure it is possible that even suboptimal use of procedures may cause complete disappearance of congestive heart failure simply because the disease is not far advanced. However, when the disease advances to a point beyond control by imperfect therapy, the optimal use of each and every procedure may be extremely important in effecting adequate control of the congestion. Suboptimal handling of the patient may result from inadequate use of procedures, from omission of procedures, or from complications to

therapy. Some of the most important of these are listed below.

Rest. In recent years there has been considerable change in the attitude on bed rest for patients with heart disease. The sitting position is obviously more comfortable from the standpoint of dyspnea and, in fact, use of a chair rather than a bed for rest is considered satisfactory. Ambulation as soon as possible is now standard for patients with congestive cardiac disease. This tends to prevent the complications of stasis. However, it is perfectly clear that excessive physical activity will lead to cardiac decompensation and that the evaluation of rest in therapy is important when the disease is refractory.

Status of Digitalization. The basic problem in the use of digitalis in congestive failure rests in careful tailoring of therapy to the individual patient. Rules of thumb commonly used in digitalization may lead to the false belief that specific doses of digitalis may be given to individuals on the basis of body weight, and the dose of the drug then dropped to a so-called maintenance level. Even with preparations such as Digitoxin, in which the absorption factor is least variable, the effect of the drug upon the individual and upon the individual's heart is variable. In all cases the dose of digitalis should be adjusted to the patient's own needs. An average amount may be given at the beginning to help saturate the patient only as a guide for further administration of digitalis to the proper level for that particular person. This must be done and the dosage adjusted upon the patient's reactions to the drug and upon the effects on the patient's circulation.

Many patients receive suboptimal doses of digitalis, their physicians believing they are administering optimal dosage. This is a very frequent cause of unsuccessful control and the lack of control may erroneously be interpreted as refractory heart failure. It can be corrected by proper adjustment of the dose.

Patients put to bed with congestive heart failure and given rest, digitalis and diuretics often respond satisfactorily. They may respond due to the rest and diuretics even though the digitalis is not given to the optimal level. However, when the patient again is permitted to be up and exercise to some degree, and the effects of rest are no longer totally operating in the maintenance of a normal circulation, the need for digitalis to the greatest point of effectiveness becomes important. This situation should be reviewed by the physician when the patient becomes "refractory."

Certain digitalis preparations, especially gitalin, appear to have a wider therapeutic range than others; and in refractory cases, when other digitalis preparations produce toxicity before therapeutic results are accomplished, gitalin may still be effective and produce improvement without toxicity.[1]

When a fibrillating heart does not slow under digitalis and the congestion generally does not respond, the presence of other factors should be suspected, including chronic infection, hyperthyroidism and active myocarditis.

Suboptimal use of digitalis may include overdosage as well as administration of too little.[1] Usually in case of excess use the signs of digitalis toxicity are present, and since they are well known such a state is usually recognized. However, there are some instances of advanced congestive heart failure, treated intensively with digitalis and without clear evidence of toxicity, in which the patient improves when the digitalis is reduced or stopped for a period of time. Intoxication from digitalis, by the production of frequent extrasystoles or tachycardia, may reduce the efficiency of the heart and precipitate congestive heart failure. When large doses of digitalis are used and the failure progresses, it is important that these aspects of the use of digitalis be reviewed and the symptoms and signs of digitalis overdosage sought out, for they are usually present as well.

The author's experiences in a large charity hospital indicate that patients with congestive heart failure are often sent in from rural areas in varying stages of digitalization. Because of the great variability in the type of preparation, the color of tablets, and the physical nature of the medication, the patient may not know that he has taken digitalis. The new observer, unaware of the fact that the patient has received some digitalis, may attempt rapid digitalization and in doing so throw the patient into digitalis intoxication. In these circumstances rapid regular heart action from digitalis block may be thought to result from the heart disease and more digitalis erroneously given.

Water. Cases in which the water content of the body is inadequate owing to therapeutic restriction of intake are not frequent now. There has been in the last several years a considerable upswing in the use of large amounts of water and control of salt intake. Water restriction may produce hypertonic dehydration. Urea and salt retention develop and changes in the kidneys may take place, as reflected by the presence of casts and red blood cells in the urine. This may lead to a state which in the past sometimes was interpreted as refractory heart failure. It is easily corrected by the administration of water.

Electrolyte Disturbances. In the past procedures to influence the electrolyte balance have not been as highly developed as they are at the present time. These measures are often very effective in the control of heart failure when those already mentioned above

are not adequate. Patients considered refractory in the past are now well handled with procedures directed at electrolyte control.[6] Some of these important changes will now be discussed.

Sodium Restriction. The control of the intake of the sodium ion, with amounts of salt reduced to one or two grams a day, is important in the management of many patients with heart failure. There is variability from patient to patient in the degree of salt restriction necessary, depending in part upon the nature and extent of disease. Some patients will lose edema on 1.0 gm. a day and gain on 2.0 gm. Some require restriction to 0.5 gm. There are differences of opinion on severe restriction of sodium and the use of mercurial diuretics in some patients. Some physicians prefer to use rigid sodium restriction to obviate the use of a diuretic. Others prefer more liberal sodium intake and a greater use of the mercurial diuretics. There are many patients for whom a choice may be elective, but for others who are more refractory to therapy both procedures are absolutely essential.

Salt restriction may result in three general difficulties. Occasionally in patients having so-called salt-losing nephritis, salt is lost excessively in the urine. If restriction is also carried out in the diet, pronounced dehydration may take place and the results of sodium lack, as described below, may occur. Secondly, a patient may take additional sodium despite dietary instructions. He may unconsciously get salt in his diet. This may happen if the instructions he has been given are not adequate and he takes sodium bicarbonate or some other sodium-containing substances which he does not consider in the category of salt. He may also take foods with much salt in them, not knowing their content; or, owing to the unpalatability of the diet low in salt, the patient may cheat. Both of these situations can be detected by determining the amount of salt in the 24-hour specimen of urine. Thirdly, the poor intake of food owing to unpalatable low sodium diets may cause anorexia and a continuing train of symptoms related to malnutrition resulting in additional refractoriness, as already mentioned.

Mercurial Diuretics. Diuretics are not always necessary in the treatment of congestive heart failure. However, their effectiveness in sweeping out water and salt has, because of their efficacy, made them one of the standard agents of treatment in refractory heart failure. Use of them may make the difference between success and failure in a program, especially if the diet is liberal in sodium.

Mercurial diuretics are quite effective as a rule. As with all drugs, there is variability in the response, owing to a number of factors.[4] These include poor absorption at the site of injection, dietary influences, age, poor renal excretion, and pathologic changes elsewhere in the body. The present discussion is not concerned with reactions to mercurial diuretics (such as sudden death from ventricular fibrillation, activation of epilepsy, and local reactions) but with the stage of refractoriness which may develop during their use. At times effectiveness of these drugs is enhanced after certain procedures. In some instances phlebotomy has acted in this way. Reports also indicate that the addition of vitamin C or pyridoxin to the material when injected may, when the special conditions to be described below do not exist, help potentiate the action of these drugs.

Without entering into the arguments concerning the action of mercurial drugs, it can be assumed that they are effective diuretics through suppression of tubular reabsorption of electrolytes. The chief of these are sodium and chloride. The concentration of sodium and chloride ion in body fluids determines, in part, the effectiveness of the action. Activity of the drug produces, depending on its relative effectiveness from person to person, a great or small loss of chloride. A variation in sodium output also occurs.

The simplest method[2] to determine the need for electrolyte studies, especially sodium, on the blood is the modified Fantus test. This test, employing silver nitrate and a dichromate solution, will give a rough index of the urinary content of sodium chloride and show need for serum electrolyte studies. Estimates of 3 gm. per liter suggest depletion of electrolyte while 4 gm. or more per liter make it unlikely that the patient is suffering from salt depletion. If low values are obtained further studies are indicated to establish sodium and chloride relationships in the blood. Depending upon their effectiveness, along with the variability in intake of these ions, a number of individual variations in the electrolyte pattern may appear as the result of the use of the mercurials. Four of these disturbances of importance are described below.

In the first place mercurials may not be effective if the heart failure itself has so reduced glomerular filtration that there is little or no electrolyte available for mercurial action in the tubules. In this circumstance there is insufficient glomerular filtrate presented to the tubules for any remarkable action by the mercurials. Here, aminophyllin given slowly by intravenous infusion, preferably an hour to an hour and a half after the mercurial diuretic is given, or even at the same time, may increase glomerular filtration sufficiently to produce enough filtrate for significant mercurial action in the tubules.

A second way in which the patient may be refractory to mercurials is frequently noted in the early stages of administration of these agents, especially in the first week of their use. At this time there may be sufficient sweeping out of chloride in the kidneys, especially if chloride intake is low, so that chloride

loss considerably exceeds sodium loss. The patient becomes hypochloremic and alkalotic. The resultant reduction in blood chloride may be great enough to make the patient refractory to the mercurial. This level is variable. Sometimes the range is in so-called low normal and is easily elevated by oral administration of ammonium chloride to make the patient again responsive to the drug. Frequently if the blood level of chloride is below 86 mEq. the patient is refractory. This state, termed hypochloremic alkalosis, may sometimes evoke some of the symptoms of the low salt syndrome described below. The patient may first lose weight rapidly. Anorexia may follow and weakness and confusion may appear. Despite the use of the mercurial drug the patient becomes waterlogged and the severity of heart failure progresses. Renal failure and uremia may appear. Clinical differentiation is often satisfactory, but where there is difficulty studies of the blood will indicate the presence of alkalosis, low chloride levels, and sodium levels which are usually within normal range. Potassium levels in the blood are generally normal or slightly decreased. Ionized calcium is reduced and signs of latent tetany may appear. Treatment is best carried out by stopping the mercurial drug and administering chloride ions with or without a cation exchange resin. Sodium chloride is not suitable. Chloride may be given as dilute hydrochloric acid, 3 to 5 cc. three or four times a day by mouth, or as large doses of ammonium chloride, 6 to 10 gm. in divided dose per day. Potassium salts must also be supplied. After the electrolyte disturbances are corrected the patient may become responsive to the mercurial diuretic again.

A third disturbance that may occur with the use of mercurial diuretics is the low salt syndrome.[3] This is usually due to the efficiency of the drugs in the face of low salt intake or occasionally in patients with salt-losing kidneys. It is important to watch for this circumstance in patients after prolonged therapy on low salt diets and such diuretics, as well as in those with profuse sweats, loss of blood, and vomiting and diarrhea. Renal disease predisposes to development of the syndrome. In this condition there is such an outpouring of sodium that hyponatremia develops. Chloride balance, often because of the administration of ammonium chloride, may remain satisfactory. Acidosis, with resultant reduction in carbon dioxide combining power, low blood sodium, and azotemia, frequently appears. A variable train of symptoms results — anorexia, nausea, vomiting, oliguria, apathy and, at times, mental aberration. Weakness, faintness, and tachycardia develop. Mental confusion occurs.

These symptoms, in varying combinations and in varying degree, may lead a physician to believe that certain other states are present. For example, if the patient is one with hypertensive heart disease, the development of oliguria and the presence of erythrocytes and albumin in the urine may lead the observer to conclude that terminal nephritis has developed. The presence of azotemia may lead him to believe that his impression is confirmed. He may then decide that the patient has reached a terminal state and that there is no therapy that would be effective. In many patients it also happens that the edema becomes considerably worse and it is often thought that the congestive heart failure can no longer be controlled even with increasing doses of drugs. Since more vigorous therapy tends to make the patient worse, the observer may also believe that the patient is moribund and not apply indicated treatment, namely infusion of hypertonic saline solution with added potassium. At times the clinical picture is that of peripheral collapse and the situation may be mistaken for myocardial infarction. If fever, dyspnea and cyanosis appear, as they often do, the combination of findings may cause the condition to be mistaken for pneumonia, and again the wrong treatment applied.

The low salt syndrome with the clinical picture as described does not necessarily mean that all patients with heart failure and low serum sodium values fall into this category. Serum sodium levels are often mildly reduced in congestive heart failure and may be more severely depressed by some of the factors intensifying the failure—infection, digitalis toxicity, low salt diets—which produce further decreases in sodium levels. Correction of these factors is important in the treatment. In some circumstances the reduction in serum sodium may reflect intracellular metabolism which has a bearing on the extracellular osmolarity. Although such processes are not well understood, they are thought to be causative factors in hyponatremia both in and outside the heart failure problem—for example, in pulmonary tuberculosis and in other debilitating states. The low sodium under such circumstances may not represent a true depletion of sodium but may represent reduction in tonicity of extracellular fluids to correspond to cellular metabolism. In these circumstances in heart failure, administration of hypertonic saline solution would merely tend to increase edema, for the body would tend to maintain the "new" reduced tonicity level, and with the fluid restriction needed to stimulate the increased concentration of salt, great thirst would appear.

In congestive heart failure, factors leading to such states of so called "chronic dilution hyponatremia" are not always clearly evident and are not well understood. The mere addition of hypertonic saline to the treatment in such circumstances may not help the refractory patient with edema and may even be harmful. The differentiation of such patients from

the low salt syndrome described above may be difficult. In both, edema may be striking. Both may have received intensive therapy with mercurials. Gradual onset, unrelated to mercurial therapy favors the chronic dilution type. If there is acute development of the symptomatic picture of the low salt syndrome, associated with circumstances that go along with its production, as well as its symptoms and signs, the probability is that hypertonic salt solution will have favorable effect.

Much confusion exists in the present status of the problem of hyponatremia and clinicians should be guided by the factors mentioned above. Even when accurate electrolyte determinations on the blood are available the problem of therapy still remains a difficult one.

In general, certain clinical facts also help in the differentiation of hypochloremic alkalosis and the low salt syndrome. Hypochloremic alkalosis is fairly frequent, rather acute in onset, follows only several doses of a mercurial after short term therapy. Underlying renal disease is not important and tetany occasionally develops. The salt depletion syndrome is not as common, generally follows more prolonged use of mercurials, is more common with underlying renal disease, and tetany is not associated.

Still of most importance is the careful watching of the patient before any of these circumstances develops, to prevent their occurrence. Preventive therapy will often eliminate these complications which at best have a high mortality.

A fourth disturbance, occurring in the absence of mercurial therapy, is chloride acidosis. It is sometimes seen during the administration of mercurials even though not resulting from them, especially when ammonium chloride has been given over a long period. It is important because of the symptoms developing from it. The picture is more common in the presence of renal insufficiency. The clinical picture is insidious in onset and is characterized by many of the symptoms seen in the low salt syndrome, such as anorexia, nausea, and vomiting, mental apathy and at times even mental confusion. It is important that chloride administration be stopped and the acidosis treated. This can be done with intravenous infusion of lactate or bicarbonate solution.

Hypochloremic acidosis is another late manifestation in heart failure related to malnutrition, renal disease and other factors. Electrolyte therapy is not successful. Diuretics should be stopped and salt is permitted in the diet. Edema may become more severe but after the electrolytic pattern is corrected, mercurials may again be given and salt restriction resumed.

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